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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/991,445	11/16/2001	Ernest G. Schutt	48175.00005	3983

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EXAMINER	
CHONG, YONG SOO	
ART UNIT	**PAPER NUMBER**
1617	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/991,445	SCHUTT ET AL.	
	Examiner	Art Unit	
	Yong S. Chong	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-14 and 16-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10, 12-14, 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

This Office Action is in response to applicant's arguments filed on 12/15/2006. Claim(s) 11 and 15 have been cancelled. Claim(s) 1-10, 12-14, 16-20 are pending. Claim(s) 1, 10, 17 have been amended. Claim(s) 1-10, 12-14, 16-20 are examined herein.

Applicant's arguments have been fully considered but found not persuasive. The rejection(s) of the last Office Action are maintained for reasons of record and modified as a result of the new claim amendments.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10, 12-14, 16-20 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of 1-12 of US Patent 6,372,195, claims 1-101 of US Patent 6,258,339, claims1-24 of US Patent 5,695,741, claims 1-38 of US Patent 5,639,443, and claims 17-22 of US Patent

5,798,091, claims 1-9, 38-73 of US Patent 5,804,162, claims 26-51 of US Patent 6,193,952 for the reasons or record.

Response to Arguments

Applicant's request to revisit this rejection after the claims have been formally allowed is noted.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham vs John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-10, 13-14, 16-18, 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider et al US Patent 5,413,774.

The instant claims are directed microbubbles comprising a membrane of surfactants entrapping at least one fluorocarbon gas and at least one modifier gas that

can comprise oxygen. The scope of the instant limitation "modifier gas" is described in paragraphs 0034, 0061-0069.

Accordingly, the scope of the term "a modifier gas" is inclusive and encompasses other gases such as oxygen, air, perfluorocyclooctane, perfluoropentane, perfluoroethane and perfluoromethane. The instant claims further require a ratio of the modifier gas to the fluorocarbon gas in the ranges of 1:100 to about 1000:1.

Schneider meets the limitations of the claimed microbubbles. Schneider teaches gas filled microvesicles that can contain a mixture of a first perfluorocarbon gas such as perflorobutane (C_4F10) and a secondary gas such as air which contains oxygen, nitrogen, CO_2. (see col 5, lines 50-56., examples 7-8, claims 1-2, col 14, lines 45, 68). The second gas of Schneider can include other perfluorocarbons such as perfluoromethane or perfluorethane. (see (col 14, lines 42-49). Schneider also teaches a membrane composed of albumin around his microvesicles (see claims 5-9).

Schneider's fluorocarbon is the same as those instantly claimed; therefore, it possesses the same functional characteristics as the instant fluorocarbon. Air, nitrogen and the like gases including other perfuorocarbons also fall within the instant genus of modifier gases. Thus, the microbubbles of Schneider contains a perfluorobutane. The microbubbles of Schneider also comprise a secondary gas including air, perfluormethane, which meets the instant limitation "modifier gas."

Schneider's microbubbles comprise a membrane composed of albumin (see col 13-14). Scheider administers his microvesicles to Rabbits thus exposing them to an external medium comprising blood and other physiological gases such as air or oxygen.

(see examples 2-4, cols 9-11). Thus, Schneider meets all structural limitations of the instant claims and all functional limitations of the instant claims.

Schneider only fails to specifically recite the instantly claimed ranges of modifier gas to fluorocarbon gas.

However, absent a showing of unexpected results, it would have been obvious to one of ordinary skill in the art at the time of invention to optimize the concentrations of individual gases in Schneider's microbubbles by routine experimentation to observe the most effective clinical results.

Claims 12, 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider et al US Patent 5,413,774 in view of Tickner US Patent 4,265,251.

The teachings of Schneider are described above. Schneider only fails to incorporate delivery of oxygen in his microbubbles.

Tickner teaches methods of ultrasound imaging using gas containing microbubbles wherein the gas is oxygen (abstract, col 7, lines 11-54). Tickner teaches that although the preferred gas is carbon dioxide, however, other gases such as freons and oxygen may be used in his contrast agents (col 6, lines 63-67).

Although Schneider fails to use oxygen with pefluorobutane in his gaseous mixtures compositions, he specifically teaches that any gas like air and nitrogen can be employed in his gaseous mixture. Tickner shows that for the purposes of ultrasonic contrast agents, gases such as oxygen, nitrogen, and Freons are substantially interchangeable and are functional equivalents.

Thus, absence of showing unexpected results, it would have been obvious to one of ordinary skill in the art at the time of invention to substitute one of air or nitrogen gases in Schneider's microvesicles with oxygen and create a microvesicle that contains pefluorobutane and oxygen, because as shown by Tickner, oxygen is considered art recognized equivalents to suitable gases enumerated by Schneider. Subsequently, the ordinary skill in the art would have had a reasonable expectation of success in mixing perfluorobutane with oxygen to produce a gaseous microvesicles.

Claims 1-10, 12-14, 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider in view of Clark US Patent 5,536,753.

The teachings of Schneider are described above. Schneider does not specifically uses oxygen in his gaseous mixture.

Clark is used to show that perflourocarbon containing emulsions are safe oxygen transport agents. (see abstract). Clark also teaches the use of emulsifying agents such as phospholipids and polymeric agents that can entrap the gas within his formulation (see col 2, lines 43-55). Clark further employs such fluorocarbons as perfluoromethylcyclohexanes that fall within the scope of the instantly claimed perfluorocyclohexanes (see col 2, lines 39 and col 4, lines 60-64). Clark further elaborates on suitable concentrations of perfluorocarbon, the surfactant and the oxygen (see col 3-4; specifically col 3, lines 23-65).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to utilize a mixture of a perfluorocarbon with oxygen, because as suggested by Schneider and Clark, the ordinary skill in the art would have had a

reasonable expectation of success in preparing microbubble for in vivo delivery of oxygen. Absence of showing unexpected results, one of ordinary skill in the art would have had a reasonable expectation of success for optimizing the concentrations of perfluorocarbon and oxygen for effective clinical or diagnostic use, when mixing the perfluorocarbon with oxygen.

Response to Arguments

Applicant argues that Schneider does not teach a membrane composed of a monolayer of surfactant since phospholipids can form liposomes.

This is not persuasive because Schneider teaches other surfactants for use in the membrane such as albumin. Examiner notes that albumin is also an example of a membrane forming surfactant disclosed by in Applicant's specification.

Applicant argues that Schneider does not disclose oxygen as the modifier gas, which diffuses through the membrane.

In response to applicant's arguments against the references, one cannot show nonobviousness by attacking references individually where the rejections are based on the combination of references. See *In re Keller*, 642 F. 2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that the final microbubbles disclosed by Schneider contain only one gas, the fluorocarbon.

This is not persuasive because Schneider clearly teaches gas filled microvesicles that contain a mixture of a first perfluorocarbon gas such as perflorobutane (C_4F10) and a secondary gas such as air which contains oxygen, nitrogen, CO_2. (see col 5, lines 50-

56., examples 7-8, claims 1-2, col 14, lines 45, 68). The second gas of Schneider can include other perfluorocarbons such as perfluoromethane or perfluorethane. (see (col 14, lines 42-49).

Applicant argues against combining the Schneider and the Tickner references since Schneider discloses microbubbles filled with "common gases such as air, methane, or CO2" will collapse" and should not be used.

This is not persuasive because this statement was taken from the background section of the Schneider reference so that a comparison can be made with past microballoons and the ones disclosed by Schneider. Furthermore, Tickner was used to show how oxygen is functionally equivalent to fluorocarbons. Even though oxygen is one of many components of air, oxygen is not the same as air. What's more, Schneider discloses modifier gases such as air, nitrogen and the like including other perfuorocarbons.

Applicant argues that the Clark reference teaches away from the instant invention because disclosed fluorocarbons such as perfluoroindane and perfluorocyclohexane have high vapor pressures, which cause gas embolism in subjects resulting in death.

This is not persuasive because Applicant has misinterpreted the reference. Because fluorocarbons such as perfluoroindane have high vapor pressures, perfluorocyclocarbons that have lower vapor pressures are necessary. Furthermore, Examiner notes that perfluorocyclohexane has been disclosed by the Applicant as a gas to be used in the instant invention. Examiner requests Applicant to explain how

perfluorocyclohexane is stable and can be used in the instant invention and then be unstable and cause gas embolism in the cited references.

Applicant argues that Clark is silent on how the fluorocarbon vapor is contained within the emulsion and that Clark requires the use of hydrophobic oils, whereas the instant invention does not. Applicant also argues that the compositions of Clark have a substantially shorter half-life than the compositions of Applicant's invention.

This is not persuasive because none of these arguments are commensurate with the scope of the claims.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

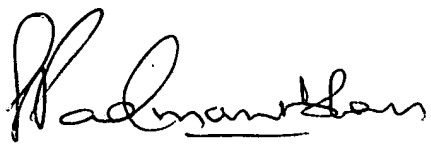
shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong S. Chong whose telephone number is (571)-272-8513. The examiner can normally be reached on M-F, 9-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SREENI PADMANABHAN can be reached on (571)-272-0629. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

YSC



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SUPERVISORY PATENT EXAMINER